

**REMARKS**

Claims 1-23 have been canceled without prejudice. Claims 24-57 are pending.

Return of initialed and dated copies of the PTO-1449 Forms previously filed, pursuant to MPEP § 609 is requested. Further copies of the documents lined-through in the PTO 1449 Forms returned with the Office Action of April 25, 2003, are attached, for the Examiner's convenience. The applicants respectfully request that the Examiner encourage the Patent Office to maintain the Patent Office files in manner that allows Patent Examiners to review cited art from related applications, as provided for in the MPEP.

Consideration of the attached documents and return of an initialed copy of the previously filed PTO 1449 Forms, pursuant to MPEP § 609, are requested.

A further Information Disclosure Statement is attached with a PTO 1449 Form listing the documents attached and referred to herein. Return of an initialed copy of the attached PTO 1449 Form, pursuant to MPEP § 609, is requested.

The Examiner is requested to acknowledge receipt by the Patent Office of the priority documents in the grand-parent application Serial No. 08/362,455, from the International Bureau with regard to PCT/EP94/01323, as evidenced by the attached Notification of Acceptance dated February 10, 1995. The Examiner is further requested to acknowledge the applicants claim to domestic priority.

The specification has been amended to include the heading "Brief Description of the Drawings" as suggested by the Examiner on page 2 of the Office Action dated April 25, 2003 (Paper No. 5). The applicants note that the undersigned's filing coversheet

dated June 5, 2001, requested an amendment of the specification on page 1, before the first line, to include the following: "This is a divisional of application Serial No. 09/638,693, filed August 15, 2000, which is a Continuation of application Serial No. 08/362,455, filed January 11, 1995, allowed, which was a 371 application of PCT/EP94/01323, filed April 27, 1994, the entire content of which is hereby incorporated by reference in this application." The Examiner is requested to ensure this amendment is entered in the application or advise the undersigned in the event anything further is required in this regard.

The specification has been amended to include the attached Sequence Listing as well as sequence identifiers corresponding therewith.

Page 33 has been amended above to correct an inadvertent typographical error. Support for the amendment may be found in, for example, Figure 5.

The applicants further note that page 39 has been amended as shown above to be consistent with amendments made in the related application Serial No. 09/638,693, and specifically, the applicants note that SEQ ID NOs:166, 168 etc., are mentioned on page 39 (penultimate and last bulleted point) of the description. SEQ ID NO:168 for instance has the sequence TCGF.....HRMA, as described in the Sequence Listing. Figure 5 indicates that the first amino acid T (thr) corresponds to amino acid 127 of the HCV polyprotein. Likewise, the last amino acid A (ala) of SEQ ID NO:168 corresponds to amino acid 319 of the HCV polyprotein (see Figure 5). The HCV Core protein spans positions 1-191 of the HCV polyprotein, the HCV E1 protein spans positions 192-383 of the HCV polyprotein. As SEQ ID NO:168 (and all other sequences of claim 87) starts at position 127, it will be understood to contain part of the Core

protein. Hence, these sequences are to be regarded as Core/E1 proteins, as amended above. SEQ ID NO:166 is one of the sequences aligned in Figure 5 and spans amino acids 1-126 of the HCV polyprotein (MSTN.....IDTL) in accordance with SEQ ID NO:166 in Sequence Listing. As the HCV Core protein spans positions 1-191 of the HCV polyprotein, SEQ ID NO:166 will be recognized by one of ordinary skill in the art as a Core protein, as amended above.

Page 40 (1st bulleted point) of the description has been amended above with regard to SEQ ID NO:192, which the Examiner will appreciate has the sequence MSTN.....WAGW, as described in the Sequence Listing. As will be clear from the description above with regard to SEQ ID NO:166, "MSTN...." refers to the start of the HCV polyprotein Core. SEQ ID NO:192 can be allocated amino acids 1-96 of the HCV Core polyprotein based on the sequence alignments in Figure 5. SEQ ID NO:192 is moreover one of the sequences aligned in Figure 5.

The specification has been further amended above on page 40 with regard to SEQ ID NOs:198 and 200. SEQ ID NOs:198 and 200 both cover the sequence CARTITT.....W(X/A)TY, as described in the Sequence Listing. SEQ ID NO:270 covers the sequence TITT.....WATY. SEQ ID NO:270 is one of the sequences aligned in Figure 7 (except for the first amino acid "T") and from Figure 7 one of ordinary skill in the art will appreciate that SEQ ID NO:270 spans amino acids 1284-1764 of the HCV polyprotein. SEQ ID NOs:198 and 200 both have 3 extra amino acids at their amino-terminus and thus span amino acids 1281-1764 of the HCV polyprotein. The common amino acids for the three SEQ ID NOs are 1284-1764.

The attached paper and computer readable copies of the Sequence Listing are the same. No new matter has been added. A separate Statement to this effect is attached.

The specification has been amended to include an Abstract, in response to the Examiner's requirement for the same at page 4 of Paper No. 5.

The amendment of the specification to include the attached Sequence Listing and the attached sheet 4 of 111 of the Figures are believed to obviate the Examiner's requirement for a new Declaration noted on page 4 of Paper No. 5. The "alterations" referred to by the Examiner were inadvertent notations apparently made during prosecution of the parent application and not removed prior to copying of the application and filing of the present application. Reconsideration and withdrawal of the objection to the specification noted on page 4 of Paper No. 5 are requested.

To the extent not obviated by the above amendments, the Section 112, second paragraph, rejection of claims 24, 26, 28, 30-40, 42, 44, 46, 48 and 50-57 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following comments. The Examiner's objections are addressed in the following in a manner presented on pages 4-5 of Paper No. 5.

(a) Initially, the applicants note that claim 24 has been amended to further specify that the recited genotype-specific nucleotide is a type 3c specific nucleotide, as will be understood by one of ordinary skill in the art. Moreover, the Examiner is urged to appreciate that the phrase "genotype-specific" is understood by those of ordinary skill in the art, as well as the Patent Office. See, attached claims of U.S. Patent Nos. 6,548,244; 5,882,852 and 5,514,539, for example, wherein the Patent Office has

granted claims reciting the objected-to phrase. The objected-to phrase is submitted to be definite.

(b) The Examiner is requested to see, for example, the specification in the paragraph spanning pages 23 and 24 wherein "primer" is defined as being, for example, 5-50 nucleotides in length. The primers specified in the application (SEQ ID NOs: 63-82, 124-125, and 141-142) all are within this range. The recitation of 8 nucleotides is supported by, for example, original claims 1 ("polynucleic acid containing 8 or more contiguous amino acids") and 6 ("composition according to any of claims 1 to 5 wherein said polynucleic acid is liable to act as a primer"). Contrary to the Examiner's assertions therefore, the objected-to term is believed to be definite from the teachings of the specification as well as the general understanding of one of ordinary skill in the art.

(c) The applicants request consideration of the above comment in ¶(b) above in response to the Examiner's objection of ¶(c) on page 5 of Paper No. 5.

(d) The Examiner is requested to see, for example, the specification in full paragraphs 4 and 5 of page 24 wherein "probe" is defined as being, for example, 5-50 nucleotides. The Examiner is also requested to see the description of primers. Interestingly, the Patent Office has, in other applicants of the assignees', not distinguished between primers and probes and rejected probes as allegedly being anticipated over art teaching primers. See, Serial No. 09/899,082 being examined by Examiner WHISENANT. The objected-to phrase is submitted to be described in the specification and will be definite to those of ordinary skill in the art.

(e) The applicants request consideration of the above comment in ¶(d) above in response to the Examiner's objection of ¶(e) on page 5 of Paper No. 5.

(f) The claims have been amended to correct the inadvertent typographical error noted by the Examiner.

(g) Claims 54-57 have been amended above to incorporate the Examiner's helpful suggestion.

(h) Claims 54-57 have been amended above to advance prosecution. The applicants submit however that the deleted phrase will be recognized by one of ordinary skill in the art as evidenced, for example, by the Wallace et al (Methods Enzymol. 152: 432 (1987), page 433, third line) cited by the Examiner which indicates that "appropriate conditions" should be used. The claims have been amended, without prejudice, to advance prosecution.

Withdrawal of the Section 112, second paragraph rejection stated on pages 4-5 of Paper No. 5 is requested.

The Section 112, first paragraph "written description" or "new matter", rejection of claims 24-57 is traversed. Basis for the claimed invention may be found throughout the specification as, for example, detailed in the following as well as explained above:

Claim 24: original claims 1 and 7 and related descriptions of the originally-filed specification;

Claim 25: original claim 2, and related descriptions of the originally-filed specification;

Claims 26 and 27: original claim 16 and specification, for example in the last paragraph on page 41 and 1<sup>st</sup> paragraph on page 42;

Claims 28-31 and 50-57: original claim 8 and specification in, for example, the 1<sup>st</sup> full paragraph of page 23, 2<sup>nd</sup> full paragraph of page 24, 1<sup>st</sup> full paragraph of page 25, 4<sup>th</sup> and 5<sup>th</sup> full paragraphs of page 26, paragraph spanning pages 28-29, and 1<sup>st</sup> full paragraph of page 29;

Claims 32-35: original claim 6 and related descriptions of the originally-filed specification;

Claims 36-39: original claim 7 and related descriptions of the originally-filed specification;

Claims 40-49: original claim 22 (combined with original claims 6-7) and related descriptions of the originally-filed specification including the last paragraph of page 24.

The Examiner's reference to "Paper No. 3" on page 6 of Paper No. 5 is not understood. A Preliminary Amendment was filed June 5, 2001 which canceled claims 1-23 and added new claims 24-57 which have been examined in Paper No. 5. Moreover, as the Examiner has returned at least partially-initialed copies of the PTO 1449 Forms filed June 5, 2001 and November 20, 2002, further clarification is requested as the Examiner appears to have received all the filed papers. Basis for the recitation of, for example, 8 or more continuous nucleotides is noted above in response to the Section 112, second paragraph, rejection.

No new matter has been added. Withdrawal of the Section 112, first paragraph, rejection stated on pages 5-6 of Paper No. 5 is requested.

The Section 112, first paragraph, rejection of claims 24-57 stated on page 6 of Paper No. 5, is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following comments.

The Examiner is urged to appreciate that the fragment of Wallace et al. quoted by the Examiner does not exclude the possibility that probes shorter than 14 bases can be found suitable for specific hybridization, see, the wording "tendency" and "probably" in said

fragment. Wallace et al. further specify that the specificity of a probe should first be determined (lines 7-8 on page 434).

In support, the applicants submit the attached two examples of successful use of probes or primers shorter than 14 nucleotides. Specifically, Majzoub et al. (1983, PNAS 258, 14061-14064; copy attached) successfully utilized 8-mer primers, and Chan et al. (1979, PNAS 76, 5036-504; copy of abstract attached) successfully utilized 10-mer probes.

As for the Examiner's comments regarding amplification with at least one primer (claims 50-57), reference is made to a primer of any of the recited claims, i.e., a genotype-specific primer. It is not an absolute requirement to use two genotype-specific primers for specific amplification of a DNA sequence. Also a genotype-specific and a universal primer (see, last full paragraph on page 25) could be used. The use of at least one genotype-specific primer is, however, an absolute requirement. In addition, the Examiner appears to view amplification too narrowly, i.e., as PCR. Amplification will be understood by one of ordinary skill in the art however as possibly being obtained with a single primer. The resulting amplification will not be exponential but linear. In a sequencing reaction for example (wherein the target DNA strand is also amplified) a single primer is used.

Withdrawal of the Section 112, first paragraph, rejection stated on page 6 of Paper No. 5 is requested.

The Section 112, first paragraph, rejection of claims 24-57 stated in the last paragraph on page 6 of Paper No. 5, is traversed. Reconsideration and withdrawal of the rejection are requested in view of the above comments and remarks with regard to the teachings of the present specification relating to "probes".



The Section 103 rejection of claims 24 and 25 over Cha (WO 92/19743) and Wallace (Methods Enzymol. 152: 432 (1987)), is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

The cited art fails to provide motivation for one of ordinary skill in the art to make and/or use the presently claimed invention. The Examiner's assertion that one of ordinary skill would have allegedly been motivated to "make and use oligonucleotide probes to any region of the DNA disclosed in Cha et al." (see, page 7 of Paper No. 5 (emphasis added)) is not supported by the cited art. The applicants submit, with respect, that the Examiner's rejection has been made with an impermissible use of hindsight.

SEQ ID NO:60 of Cha et al. (WO92/19743), referred to by the Examiner, is of genotype GII according to the HCV classification system used by Cha et al. According to the HCV classification system of the current application, SEQ ID NO:60 is a HCV genotype 1b sequence (see Table 3 on page 11 of the current application). SEQ ID NO:147 of the current invention, referred to by the Examiner, is of HCV genotype 3c, a new subtype that was moreover identified and classified for the first time in the current invention. Only when SEQ ID NO:147 was available could this sequence be compared with sequences from other HCV types and could the classification of this sequence as a HCV type 3c sequence be made. It would not have been obvious to make and use a genotype 3c sequence from the teachings of Cha and Wallace as, prior to the current invention, the HCV genotype 3c was not yet known. Moreover, as HCV type 3c probes and primers can only be designed after the discovery of the same by the present

applicants, the cited art fails to teach or suggest the presently claimed invention. In addition, the at least 8 contiguous nucleotides as recited in claims 24 and 25 must contain at least one genotype-specific nucleotide of the HCV type 3c sequence. The 43-nt fragment of SEQ ID NO:60 of Cha et al. is not believed to include this requirement and thus does not suggest the presently claimed invention. The combination of Cha with Wallace et al. (1987; Methods Enzymol. 152, 432) is not believed to cure these deficiencies of Cha.

Withdrawal of the Section 103 rejection of claims 24 and 25 over Cha in view of Wallace is requested.

The Section 103 rejection of claims 28-57 over Cha (WO 92/19743) and Wallace (Methods Enzymol. 152: 432 (1987)) and "the applicants' admitted state of the prior art (instant application at page 24)", is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

The cited art fails to provide motivation for one of ordinary skill in the art to make and/or use the presently claimed invention. The Examiner's assertion that one of ordinary skill would have allegedly been motivated to "assemble the various reagents needed to perform the above-mentioned procedures [i.e., "to amplify the nucleic acids in a manner admitted to be old"? see, sentence spanning pages 7-8 of Paper No. 5] into a kit for mere convenience (claims 50-57)" (see, page 8 of Paper No. 5), is not supported by the cited art. The applicants submit, with respect, that the Examiner's rejection has been made with an impermissible use of hindsight.

As noted above, the combination of Cha and Wallace fails to support a *prima facie* case of obviousness of claims 24 and 25. Each of the further rejected claims (i.e.,

claims 28-57) further define or provide for uses of the invention described in claims 24 and/or 25. The further defined products and uses of the noted dependent claims would not have been obvious "merely" because similar uses and/or kits may have been known which contained and/or used products different from the invention of claims 24 and/or 25. See, for example, *in re Brouwer*, 37 USPQ2d 1663 (Fed. Cir. 1996) and *In re Ochiai*, 37 USPQ2d 1127 (Fed. Cir. 1995) as well as the Commissioners Notice published at 1184 OG 86, on March 26, 1996 and the related TRAINING MATERIALS FOR TREATMENT OF PRODUCT AND PROCESS CLAIMS IN LIGHT OF *IN RE BROUWER* AND *IN RE OCHIAI* AND 35 U.S.C. 103(b). Without more, the Section 103 rejection of claims 28-57 should be withdrawn.

For completeness, the applicants note that it could not have been obvious to assemble the various recited reagents (i.e., type-specific nucleic acids, probes and/or primers) prior to the invention of such type-specific nucleic acids by the present applicants.

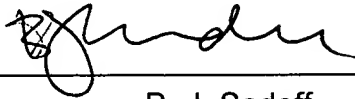
Withdrawal of the Section 103 rejection of claims 28-57 is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is urged to contact the undersigned, preferably by telephone, in the event anything further is required.

**MAERTENS et al.**  
Serial No. 09/873,224

Respectfully submitted,

**NIXON & VANDERHYE P.C.**

By:   
B. J. Sadoff  
Reg. No. 36,663

BJS:  
1100 North Glebe Road, 8th Floor  
Arlington, VA 22201-4714  
Telephone: (703) 816-4000  
Facsimile: (703) 816-4100